

Patent

**BLOOD COLLECTION SYSTEMS AND METHODS
USING A POROUS MEMBRANE ELEMENT**

Related Applications

This application is a divisional of co-pending
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Field of the Invention

The invention generally relates to blood
collection and processing systems and methods.

10 **Background of the Invention**

Systems composed of multiple, interconnected
plastic bags have met widespread use and acceptance in
the collection, processing and storage of blood
components. Using these systems, whole blood is collected
15 and separated into its clinical components (typically red
blood cells, platelets, and plasma). The components are
individually stored and used to treat a multiplicity of
specific conditions and diseased states.

Before storing blood components for later
20 transfusion, it is believed to be desirable to minimize
the presence of impurities or other materials that may
cause undesired side effects in the recipient. For
example, because of possible reactions, it is generally
considered desirable to remove substantially all the
25 leukocytes from blood components before storage, or at

least before transfusion.

Filtration is conventionally used to accomplish leuko-reduction. Systems and methods for reducing the number of leukocytes by filtration in multiple blood bag configurations are described, e.g., in Stewart U.S. Patent 4,997,577, Stewart et al. U.S. Patent 5,128,048, Johnson et al. U.S. Patent 5,180,504, and Bellotti et. al. U.S. Patent 5,527,472.

Summary of the Invention

One aspect of the invention provides systems and methods for removing leukocytes from blood using a filter media having a main filter region comprising a porous membrane structure extending between first and second skin surfaces. The porous membrane structure is formed by intersecting cells having a range of diameters. The cells adjacent to the first skin surface have diameters generally smaller than the diameters of the cells adjacent to the second skin surface. The first skin surface includes an open area defined by pores, which are formed by the intersection of cells with the first skin surface. The majority of the open area is defined by pores having a diameter of between about 12 μ m and 28 μ m.

In one embodiment, the main filter region includes a polyethersulfone material.

In one embodiment, the filter media is enclosed in a housing. The housing comprises first and second flexible sheets made of a meltable material. A peripheral seal joins the sheets directly to the filter media to encapsulate the filter media between the first and second sheets. The seal includes a commingled melted matrix comprising material of the sheets and material of the filter media.

Another aspect of the invention provides systems and methods for removing leukocytes from blood using a filter media having a main filter region. The

main filter region comprises a layered porous membrane structure that includes several regions of larger pore sizes alternating in the direction of flow with several regions of smaller pore sizes, or vice versa. Blood
5 traversing the main filter region thereby passes in succession through several alternating regions of smaller, then larger, then smaller diameter pores, or vice versa.

Other features and advantages of the invention
10 will become apparent upon review of the following description, drawings, and appended claims.

Brief Description of the Drawings

Fig. 1 is a schematic view of a blood collection and storage system that includes a filter that
15 embodies features of the invention and that removes leukocytes from red blood cells;

Fig. 2 is an exploded perspective view of the filter that forms a part of the system shown in Fig. 1;

Fig. 3 is an assembled perspective view of the
20 filter shown in Fig. 2;

Fig. 4 is a side section SEM (x900) view showing a membrane that the filter shown in Fig. 3 incorporates as its main filter for removing leukocytes;

Fig. 5 is a plane SEM view (x400) of the
25 downstream skin surface of the membrane shown in Fig. 4; and

Fig. 6 is a plane SEM view (x1.5k) of the upstream skin surface of the membrane shown in Fig. 4;

Fig. 7 is a side section view of the pre-
30 assembled form of the filter shown in Fig. 3, located between two spaced apart radio frequency energy dies;

Fig. 8 is a side section view of the pre-assembled form of the filter shown in Fig. 3, engaged by the dies, which apply radio frequency energy to form a
35 unitary peripheral seal;

Fig. 9 is a schematic view of a blood collection and storage system that includes two integral filters that embody features of the invention, one to remove leukocytes from red blood cells and the other to
5 remove leukocytes from platelet-rich plasma; and

Fig. 10 is a schematic view of a blood collection and storage system that includes a filter that embodies features of the invention to remove leukocytes from whole blood prior to centrifugal processing.

10 The invention is not limited to the details of the construction and the arrangements of parts set forth in the following description or shown in the drawings. The invention can be practiced in other embodiments and in various other ways. The terminology and phrases are
15 used for description and should not be regarded as limiting.

Description of the Preferred Embodiments

Fig. 1 shows a blood collection and storage system 10 having an integral flexible filter 20. The
20 filter 20 can be incorporated into various types of blood collection systems, and representative examples of such systems will be described.

In Fig. 1, the system 10 provides red blood cells for long term storage that are substantially free
25 of leukocytes. The system 10 also provides platelet concentrate and the platelet-poor plasma for long term storage. The blood collection and storage assembly 10, once sterilized, constitutes a sterile, "closed" system, as judged by the applicable standards in the United
30 States. The system 10 is a disposable, single use item.

As shown in Fig. 1, the system 10 includes a primary bag 12 and three transfer bags or containers 14, 16, and 18. Like the flexible filter 20, the transfer bags 14, 16, and 18 are integrally attached to the system
35 10.

In use, the system 10 is manipulated in conventional ways. The primary bag 12 (which is also called a donor bag) receives whole blood from a donor through integrally attached donor tube 22 that carries an
5 phlebotomy needle 24. A suitable anticoagulant A is contained in the primary bag 12. The whole blood is centrifugally separated by conventional means inside the primary bag 12 into red blood cells and platelet-rich plasma. Leukocytes dwell in the interface between the red
10 blood cells and platelet-rich plasma.

The transfer bag 14 is intended to receive platelet-rich plasma separated from the whole blood collected in the primary bag 12. Attempts are made when transferring the platelet-rich plasma out of the primary
15 bag 12 to keep as many leukocytes in the primary bag 12 as possible. The transfer of platelet-rich plasma into the transfer bag 14 leaves the red blood cells and the leukocytes behind in the primary bag 12.

The transfer bag 16 contains a suitable
20 storage solution S for red blood cells. One such solution is disclosed in Grode et al U.S. Patent 4,267,269, which is sold by Baxter Healthcare Corporation under the brand name ADSOL® Solution. The storage solution S is transferred into the primary bag 12 after transfer of the
25 platelet-rich plasma into the transfer bag 14.

The platelet-rich plasma is centrifugally separated by conventional means in the transfer bag 14 into platelet concentrate and platelet-poor plasma. The platelet-poor plasma is transferred into the transfer bag
30 16, which is now emptied of storage solution S. The transfer bag 16 serves as the storage container for the platelet-poor plasma. The transfer bag 14 serves as its storage container for the platelet concentrate.

The storage solution S is mixed with the red
35 blood cells and leukocytes remaining in the primary bag

12. The mixture of storage solution S, red blood cells, and leukocytes is transferred from the primary bag 12 through tubing 26. The tubing 26 carries in-line the integral, flexible filter 20. The flexible filter 20 includes a filtration medium 28 contained within a housing 30. The filtration medium is selected to remove leukocytes from red blood cells.

The leukocyte-reduced red blood cells enter the transfer bag 18. The transfer bag 18 serves as the storage container for the leukocyte-reduced red blood cells. Prior to storage, residual air in the transfer bag 18 can be vented into the primary bag 12 through tubing 60.

The bags and tubing associated with the processing system 10 can all be made from conventional approved medical grade plastic materials, such as polyvinyl chloride plasticized with di-2-ethylhexyl-phthalate (PVC-DEHP). The bags are formed using conventional heat sealing technologies, e.g., radio frequency (RF) heat sealing.

Alternatively, since the transfer bag 14 is intended to store the platelet concentrate, it can be made of polyolefin material (as disclosed in Gajewski et al U.S. Patent 4,140,162) or a polyvinyl chloride material plasticized with tri-2-ethylhexyl trimellitate (TEHTM). These materials, when compared to DEHP-plasticized polyvinyl chloride materials, have greater gas permeability that is beneficial for platelet storage.

The flexible filter 20, like the rest of the system 10, is a disposable, single use item. Also, like the rest of the system 10, the filter housing 30 is made using conventional approved medical grade plastic materials. Furthermore, like the rest of the system 10, the filter housing 30 is formed using conventional radio frequency heat sealing technology. The filter 20, being

flexible, facilitates handling and reduces the incidence of damage to other components of the system 10 during centrifugal processing.

5 In the illustrated embodiment (see Figs. 2 and 3), the filter housing 30 comprising first and second sheets 32 and 34 of medical grade plastic material, such as polyvinyl chloride plasticized with di-2-ethylhexylphthalate (PVC-DEHP). Other medical grade plastic materials can be used that are not PVC and/or are DEHP-free, provided that the material heats and flows when
10 exposed to radio frequency energy.

As Fig. 2 best shows, the filtration medium 28 comprises, in the blood flow direction, a prefilter region PRF, a transfer filter region TRF, a main filter region MF, and a postfilter region POF. The regions are
15 sandwiched between the sheets 32 and 34 and joined along a continuous peripheral seal 36 (as Fig. 3 shows).

The prefilter region PRF and postfilter region POF can be made of fibrous material, e.g., include melt blown or spun bonded synthetic fibers (e.g., nylon or polyester or polyethylene or polypropylene), semi-synthetic fibers, regenerated fibers, or inorganic fibers. The prefilter and postfilter regions PRF and POF desirably have a pore size and fiber diameter not well
20 suited for leukocyte removal. Instead, the fibrous material of the prefilter region PRF is sized to remove gross clots and aggregations present in the blood. The fibrous material of the postfilter region POF is sized to provide a fluid manifold effect at the outlet of the
25 filter. In a representative embodiment, the material of the prefilter region PRF has a pore size of between about 15 μm to about 20 μm , and the material of the postfilter region POF has a pore size of about 20 μm .

The transfer region TR is made of fibrous
35 material (e.g., polyethylene) having a fiber diameter

less than the fiber diameter of the prefilter region PRF.

In a representative embodiment, the material of the prefilter region PRF possesses an average fiber diameter of about 12 μm , and the material of the transfer filter region TFR possesses a fiber diameter of about 4 μm . Preferably, the fibrous material of the transfer filter region TFR is also coated with a polymer material including polyalkylene oxide (PEO), such as disclosed in US Patent 6,045,701, which is incorporated herein by reference.

Preferably, the fibrous material of the transfer region TFR is arranged in more than a single layer. In a preferred embodiment, a transfer filter region TFR comprises four formed layers, each having an individual thickness in the flow direction of about 0.4 mm.

The main filter region MF comprises a membrane 100 that removes leukocytes. With reference to Figs. 4 to 6, the membrane 100 of the main filter region MF can be characterized as follows:

(i) as Fig. 4 shows, in side section, the membrane 100 possess an interior porous structure formed by intersecting cells 102 having a range of diameters, with interior apertures 104 formed by intersections of the cells 102,

(ii) as Fig. 4 also shows, the diameters of the cells 102 can be grouped into two general regions: larger diameter cells 102 adjacent to one skin surface 108 (which Fig. 6 shows in plane view) and smaller diameter cells 102 adjacent to the other skin surface 106 (which Fig. 5 shows in plane view). It is not believed important as to whether the blood flow is from skin surface 108 to 106, or vice versa,

(iii) as Fig. 5 shows, the cells 102 intersect the skin surface 106, forming pores 110, and

(iv) the majority of the skin surface 106 occupied by the pores 110 (i.e., the total open area of the skin surface 106 shown in Fig. 5) is formed by pores 110 having a diameter of between about 12 μm to about 28 μm .
5

Alternatively, the main filter region MF can comprise alternating layers of isotropic membranes of small and large pore size. The main filter region MF thus comprises a layered porous membrane structure that
10 includes regions of larger pore sizes alternating in the direction of flow with regions of smaller pore sizes, or vice versa. Blood traversing the main filter region thereby passes in succession through alternating regions of smaller, then larger pores, or vice versa.

15 In a preferred embodiment, the membrane 100 is made of a polyethersulfone (PES) material, which can be obtained from Osmonics, Inc. (Minnetonka, Minnesota).

To achieve a 3 to 4 log reduction in the number of leukocytes carried in unit of whole blood
20 (typically between 2×10^9 to 6×10^9) without plugging, the total surface area of the membrane 100 forming the main filter region MF should be between about 500 cm^2 and about 1500 cm^2 .

In a preferred arrangement, PES membranes 100
25 are arranged in multiple individual layers, each individual layer having the characteristics listed above, which together forming the main filter region MF. Blood traversing the multiple layers of the main filter region MF thereby encounter alternating regions of large pore
30 size and then small pore size and then large pore size and then small pore size, etc, or vice versa. This serial transition between large and small pore size regions along the flow path create successive changes in the flow dynamics of the blood and are believed to enhance
35 leukocyte removal.

The assembly of the layered PES membranes in the main filter region MF, in association with a prefilter region PRF, a transfer filter region TFR, and a postfilter region POF, as above described, provides a
5 filter 20 that allows the passage of upwards to 90% to 95% of platelets contained in a unit of whole blood, while achieving a 3 to 4 log reduction in the number of leukocytes. The filter 20 is therefore well suited for inclusion in multiple blood bag systems in which whole
10 blood is filtered to remove leukocytes before centrifugation, as will be described.

In forming the filter 20, a unitary, continuous peripheral seal 36 (see Fig. 3) is formed by the application of pressure and radio frequency heating
15 in a single process to the two sheets 32 and 34 and filtration medium 28. The seal 36 joins the two sheets 32 and 34 to each other, as well as joins the filtration medium 28 to the two sheets 32 and 34. The seal 36 integrates the material of the filtration medium 28 and
20 the material of the plastic sheets 32 and 34, for a reliable, robust, leak-proof boundary. Since the seal 36 is unitary and continuous, the possibility of blood shunting around the periphery of the filtration medium 28 is eliminated.

25 The filter 20 also includes inlet and outlet ports 38 and 40 (see Fig. 3). The ports 38 and 40 comprise tubes made of medical grade plastic material, like PVC-DEHP. As Fig. 2 shows, the ports 38 and 40 comprise separately molded parts that are heat sealed by
30 radio frequency energy over a hole 40 formed in the sheets 32 and 34 before the unitary peripheral seal 36 is formed.

The filter 20 (see Fig. 7) is formed by sandwiching layers of the prefilter region PRF, transfer
35 filter region TFR, main filter region MF, and postfilter

region POF between the first and second plastic sheets 32 and 34. The layered filter pre-assembly is placed between a pair of opposed dies 50 and 52 (as Fig. 7 shows). The opposed dies 50 and 52 are moved together (see Fig. 8),
5 to apply pressure to press the peripheral edge of the pre-assembly 48 together. Preferably a stop 54 is provided to accurately space the dies 50 and 52 apart from each other.

As the dies 50 and 52 apply pressure about the
10 peripheral edge, RF energy is applied through the dies 50 and 52. The combination of RF energy and pressure softens the plastic material of the sheets 32 and 34. The applied pressure causes the heat softened material of the sheets 32, 34 to penetrate the interstices of the filtration
15 medium 28, creating an interior matrix of sheet material commingled with filtration medium material. Within the matrix, the filtration medium melts, creating a composite seal 36.

At its surface, along the sheets 32 and 34,
20 the seal 36 comprises mostly the material of the sheets 32 and 34. With increasing distance from the surface, the seal 36 comprises a commingled melted matrix of the material of the sheets 32 and 34 and the material of the filtration medium 28. This is believed to occur because
25 the sheet material, which is electrically heated and caused to flow by the applied radio frequency energy, is further caused by the applied pressure to flow into and penetrate the interstices of the medium 28. The heated sheet material that flows under pressure into the
30 interstices of the medium 28 causes the medium 28 itself to melt about it.

After a brief period of cooling, the seal 36 sets and the dies 50 and 52 are withdrawn. In a representative embodiment, the dies 50 and 52 are
35 coupled to a 4 KW radio frequency energy generator.

Pressure of 60 PSI is applied, maintaining a die gap of 1.2 mm. A sealing time of about 5.5 seconds is realized, followed by a cooling time of about 5 seconds.

5 A flexible filter can be integrated in different ways into multiple blood bag systems. For example (see Fig. 9), a system 10' like that shown in Fig. 1 can include a second integral flexible filter 20' in-line between the primary bag 12 and the transfer bag 14. In this arrangement, the filtration medium 28' is
10 selected to remove leukocytes from platelet-poor plasma prior to entering the transfer bag 14.

As another example, Fig. 10 shows a system 70 that includes a primary bag 72 and transfer bags 74, 76, 78. The primary bag 72 receives whole blood from a donor.
15 The whole blood is transferred from the primary bag 72 through tubing 80 into the transfer bag 74. The tubing 80 carries in-line an integral, flexible filter 82 of the type previously described. The filtration medium 84 is selected to remove leukocytes from the whole blood,
20 without also removing platelets or red blood cells. The leukocyte-depleted whole blood is centrifugally processed in the transfer bag 74 into red blood cells and platelet-rich plasma, both of which are in a leukocyte-depleted condition.

25 The transfer bag 76 receives the leukocyte-depleted platelet-rich plasma, leaving the leukocyte-depleted red blood cells in the transfer bag 74 for storage. The platelet-rich plasma is centrifugally separated by conventional means in the transfer bag 76
30 into platelet concentrate and platelet-poor plasma. The platelet-poor plasma is transferred into the transfer bag 78 for storage. This leaves the platelet concentrate in the transfer bag 76, which serves as its storage container.

35 The flexible filter that embodies the

invention avoids the handling and processing problems rigid filter housings have presented in the past. Unlike a rigid housing, the flexible housing 30 will not puncture associated bags, which are also made of flexible plastic materials. Unlike a rigid housing, the flexible housing 30 conforms and is compliant to stress and pressures induced during use.

The close proximity of the flexible sheet 32 and the filtration medium 28 on the inlet side of the filter 20 creates a capillary effect, which promotes displacement of air and automatic priming of the filter 30 under the fluid head pressure of gravity flow from a source container. The fluid head pressure causes the flexible sheet 32 to distend or expand after priming. It thus creates a natural pressure manifold, which evenly distributes the fluid across the inlet face of the filtration medium 28. This assures that entrapped air is vented and that the fluid flows through the filtration medium 28 under uniform pressure and distribution.

As the fluid container empties, negative pressure is created downstream of the filter 20. Because the inlet and outlet sheets 32 and 34 of the housing 30 are flexible, they will collapse around the space occupied by the filtration medium 28, minimizing the amount of residual blood left in the filter 30 after use. Fluid drains from the outlet side without the use of an auxiliary air vent.

Furthermore, the flexible housing 30 will not crack during heat sterilization. The flexible housing 30 also does not impede heat penetration during heat sterilization processes. Instead, the housing 30 accommodates uniform heat penetration into the filtration medium 28. The filter 20 can undergo sterilization at the same time the entire system 10 is sterilized, making a one-step sterilization process possible.

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- 14 -

Various features of the invention are set forth in the following claims.